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A Risk Prediction Model for Delayed Graft Function in Deceased Donor Kidney Transplantation

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Abstract

Delayed graft function is commonly defined as the need for dialysis in the first seven days post-kidney transplantation. It occurs in approximately 25% of deceased donor kidney transplants, although the incidence varies depending on the risk profile of the donor and recipient. Risk assessment has become increasingly important in the medical community as a tool to inform protocol decisions and resource allocation, and risk assessment for delayed graft function is no exception. Delayed graft function deals a double blow by incurring both clinical and economic penalties. A risk prediction model for delayed graft function was recently developed in deceased donor kidney transplantation that quantifies a large number of risk factors, each of which is independently associated with delayed graft function. As the criteria for acceptable donor kidneys expand, the use of higher-risk donors will undoubtedly provide lifesaving organs to critically ill patients, but at a significant cost. The incidence of delayed graft function in renal transplantation will undoubtedly increase with the use of "marginal donors". A balance must be struck by minimizing the occurrence of delayed graft function without rejecting marginal donor organs with reasonable prognoses for survival. The delayed graft function risk model has applicability as a tool for defining individuals or patient groups at increased risk, or designing clinical trials whose objective is to evaluate the impact of immunosuppressive strategies or novel agents on the development of delayed graft function. The model should not be used as a basis for clinical decision making per se, but as a tool to complement the decision making process.

The clinical utility of the delayed graft function risk model is further discussed in this review.

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Key words

Delayed graft function. Risk prediction. Kidney transplantation. Clinical utility. Risk calculator.

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Introduction

Medical decisions on healthcare strategies and resource planning depend on predicting the course of disease and the likely effects of alternative treatments on that course. The predictions anticipate the likely trajectory of the patient's health as a result of the various strategies available to the clinician. A classic example is the Framingham Risk Score, which is useful for deciding when to initiate lifestyle modification and preventive medical treatment, and for patient education, by identifying men and women at increased risk for future cardiovascular events[1-3].

With the growing cost of healthcare, more attention is now focused on resource allocation in the healthcare system. The quantification of risk factors relative to resource utilization will become imperative as resources decline in managed healthcare organizations. Resource allocation in solid organ transplantation is more complicated than in many other areas of medicine because of the requirement for a scarce resource (the transplanted organ) and the high cost of each procedure. Renal transplantation differs from heart and liver transplantation because an effective therapy (dialysis) is widely available and is the standard of care for end-stage renal disease. Therefore, patients and healthcare providers have to make choices to optimize both the efficacy and safety of patient management.

Historically, acute rejection (AR) was the principal clinical challenge following renal transplantation and a primary determinant of transplant outcome. With the introduction of modern immunosuppressive regimens (e.g. antithymocyte globulin [rabbit], calcineurin inhibitors, etc.), the frequency of AR episodes following deceased donor kidney transplantation has been reported at less than 20%[4,5]. Increasing attention is being focused on a more common obstacle to successful renal transplantation, delayed graft function (DGF).

Delayed graft function

Delayed graft function is most commonly defined as the need for dialysis in the first seven days post-renal transplantation[6-8] and has been reported to occur in approximately 25% of deceased donor transplants in the USA. The incidence of DGF can vary depending on the risk profile of the donor and recipient[9,10], preservation method[11], and transplant center[12]. The etiology of DGF is not well understood, but is likely due to immunologic and nonimmunologic components. Ischemia/reperfusion injury of an allograft during the transplant procedure causes a cascade of molecular events, leading to apoptosis, inflammation, and tissue damage, resulting in organ dysfunction[13,14]. There is evidence that these immunologic events can upregulate the immune response and, thus, increase organ alloreactivity, resulting in a greater probability of AR[13,15].

Delayed graft function and AR have each been shown to impact both short-term renal function and long-term graft survival[16,17], and economic costs due to prolonged patient hospitalization and costly patient management (e.g. dialysis)[18]. In patients with early (within six months posttransplantation) acute rejection, DGF reduced kidney allograft half-life by approximately 38% (12.9 to 8.0 years) with a similar reduction in allograft half-life observed in patients having no evidence of early AR (9.4 to 6.2 years)[6]. Moreover, a kidney allograft with DGF and early AR has a half-life of 7.1 years compared with a half-life of 14.1 years for a kidney without DGF or AR[17]. The independent contribution of DGF to graft outcome is important because it indicates that eliminating only AR will not assure optimal graft survival[9]. In fact, while renal AR incidence has decreased dramatically over the past 10 years, DGF rates have decreased from about 29 to only 23%[19].

Strategies that increase the likelihood of immediate graft function and reduce the incidence of AR may result in improved renal function and long-term graft survival in kidney transplant patients. The impetus to develop effective therapies for DGF is fuelled by the growing trend of transplanting kidneys from expanded criteria donors, donation after cardiac death donors, and other "marginal" donors[20]. As the criteria for acceptable donor kidneys expand, the use of higher-risk donors will undoubtedly provide lifesaving organs to critically ill patients, but at a significant cost. The incidence of DGF in renal transplantation will undoubtedly increase with the use of "marginal donors". Clearly, a balance must be struck by minimizing the occurrence of DGF without rejecting marginal donor organs with reasonable prognoses for survival[9]. One approach is to target patients at risk for DGF and administer appropriate preventative interventions.

Risk factors for delayed graft function

A number of risk factors for DGF, in both the donor and the recipient, have been identified in patients undergoing deceased donor kidney transplantation[6,7,9-11,21-23]. The identified risk factors can be generally classified into two main categories[9,10]: (i) factors related to donor quality (e.g. donor age ≥ 50 years, prolonged cold ischemia time, cause of death, organ preservation, expanded criteria donors, and donation after cardiac death); and (ii) factors related to recipient/immunologic characteristics (e.g. poor HLA matching, peak panel reactive antibody, transfusions, prior transplants, male gender).

Predicting risk of delayed graft function

Risk assessment is increasingly used in the medical community as a tool to inform protocol decisions and resource allocation. Delayed graft function deals a double blow by incurring both clinical and economic penalties[9]. A donor scoring system based on a small cohort of patients was developed to quantify several donor risk factors (e.g. cause of death, history of hypertension) to determine early (day 30 posttransplant) graft function, and assist in "marginal" donor allocation[24]. In 2003, Irish, et al. developed a nomogram (a graphical representation of a multivariable prediction model) that quantified a large number of risk factors, each of which demonstrated predictive discrimination and were independently correlated with DGF[9].

Since the development of the DGF prediction model in 2003[9], there have been significant advances in the field of transplantation with regard to both immunosuppression and organ allocation strategies[25]. These changes may have important implications for prediction of DGF and, in light of this, the original model was refined using more recent data reported to the United Network for Organ Sharing (UNOS) database between 2003 and 2006[10]. A comparison of the old model provides a basis for understanding the changes in the relative impact of risk factors over time (Table 1). While the relative impact of most risk factors remained consistent with the original model, the relative impact of peak panel-reactive antibody and history of previous transplants diminished by 56 and 65%, respectively, while the relative impact of donor terminal serum creatinine increased by 154%. The attenuated effects of these variables may be due, in part, to improvement in the sensitivity of HLA antibody testing, optimization of immunosuppression regimens, and greater use of antibody induction[10]. However, this is offset by a greater contribution of the relative impact of donor renal function, possibly as a result of the increased use of "marginal" donors[10]. Thus, the DGF rate has remained relatively constant over time.

Table 1. Predictive models for delayed graft function based on the 2003 and 2010 Models

Variable	2003 Predictive Model[9]			2010 Predictive Model[10]		
		95% CI for OR			95% CI for OR	
	Odds Ratio (OR)	Lower	Upper	Odds Ratio (OR)	Lower	Upper
Recipient						
– Race/ethnicity: black vs. non-black	2.807	1.583	4.975	1.266	1.183	1.354
– Gender: male vs. female	1.310	1.199	1.430	1.454	1.361	1.555
– Previous transplants: yes vs. no	1.469	1.299	1.662	1.144	1.031	1.269
– Diabetes vs. other disease	1.242	1.120	1.377	1.319	1.228	1.417
– Peak PRA (per % increase)	1.007	1.005	1.009	1.003	1.002	1.004
– Pretransplant transfusions	1.153	1.057	1.257	1.252	1.167	1.343
– HLA mismatches (per unit increase)	1.077	1.050	1.105	1.046	1.028	1.064
– BMI (per unit increase)				1.043	1.037	1.049
– Duration of dialysis (per day increase)				1.001	1.000	1.000
– Duration of dialysis - squared				1.000	1.000	1.000
Donor						
– Donor age (per year increase)	1.018	1.015	1.021	1.017	1.014	1.019
– CIT (per hour increase)	1.040	1.035	1.046	1.041	1.036	1.045
– WIT (per minute increase)	1.000	1.000	1.000	1.007	1.005	1.010
– DCD vs. brain death	3.153	2.245	4.430	3.063	2.614	3.589
– History of hypertension	1.322	1.179	1.483	1.303	1.205	1.410
– Terminal serum creatinine (per unit increase)	1.230	1.150	1.315	1.693	1.579	1.815
– Donor cause of death: anoxia vs. other	1.223	1.053	1.421	1.226	1.114	1.349
– Donor cause of death: CV/stroke vs. other	1.163	1.043	1.296	1.210	1.119	1.310
– Weight (per kg increase)				0.898	0.984	0.995
– Weight - squared				1.000	1.000	1.000

Odds ratio (OR) = Odds of DGF/Odds of no DGF. PRA: panel reactive antibody; BMI: body mass index in kg/m^2; CIT: cold ischemia time; WIT: warm ischemia time; DCD: donation after cardiac death; CV: cerebrovascular cause of death *(adapted from: Irish, et al. J Am Soc Nephrol. 2003[9] and Irish, et al. Am J Transpl. 2010)[10].*

A web-based tool was developed to enhance the utility, accessibility and functionality of the updated DGF model (www.transplantcalculator.com/DGF)[10]. Donor, recipient, and transplant-related information specific to individual patients or patient populations can be entered into the interactive tool to obtain a predicted probability of developing DGF.

The tool can also be used to evaluate the relative impact of changing levels of a risk factor on the predicted odds of DGF while holding other risk factors constant. This is particularly important as some of the risk factors in the model are potentially modifiable. For example, prolonged cold ischemia time (CIT) is an important risk factor for DGF. If we decrease the cold time by five hours, we could

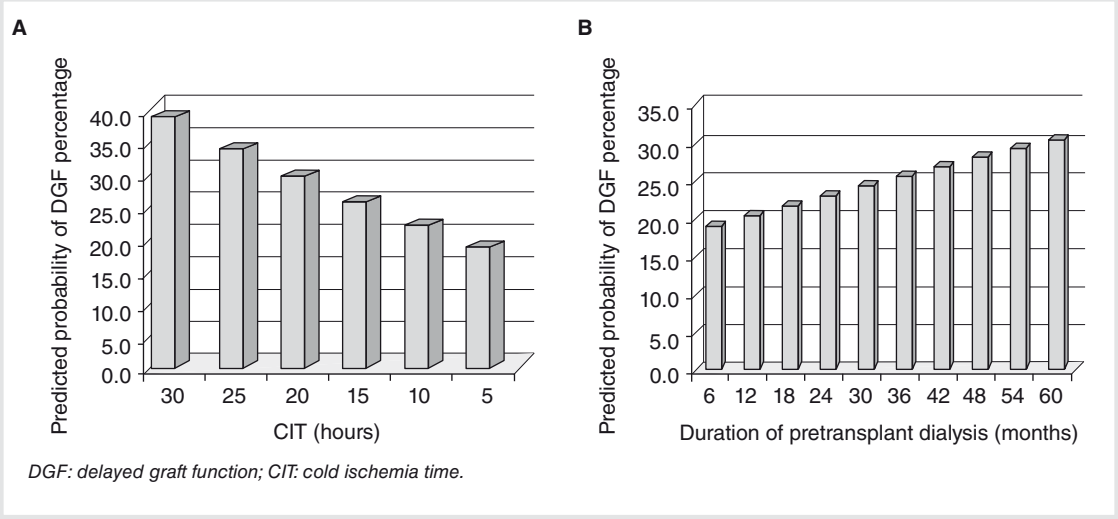

Figure 1. ***A:*** *predicted probabilities of delayed graft function for different values of cold ischemia time. A graph depicting model-based predictions of the probability of delayed graft function (y-axis) across different levels of cold ischemia time (hours)(x-axis). This graph illustrates the relationship between predicted probabilities of delayed graft function and cold ischemia time.* ***B:*** *predicted probabilities of delayed graft function for different values of pretransplant duration of dialysis (months). A graph depicting model-based predictions of the probability of delayed graft function (y-axis) by different values for duration of dialysis prior to kidney transplantation (x-axis). This graph illustrates the relationship between predicted probabilities of delayed graft function and duration of dialysis pretransplant.*

potentially decrease the odds of DGF by approximately 18% (OR: 0.82 per 5 hour change in CIT) while holding all other factors in the model constant. Figure 1 A provides the predicted probabilities of DGF for different values of CIT with all other risk factors in the model set the national average. A similar plot for varying durations of pretransplant dialysis is provided in figure 1 B. To put the model into clinical perspective, most deceased donor recipients of a primary transplant will have been on dialysis prior to transplant for three years, had an average CIT of 18 hours, a donor of 37 years of age with a terminal serum creatinine of 1.0 mg/dl, an HLA mismatch of 3, and had received a transplant transfusion. If there are no additional penalties, the recipient would be considered low-risk, with a 15% risk of developing DGF (average predicted risk of DGF is 24%).

The model has been validated using an external dataset and has been shown to have good agreement across different levels of DGF risk (Fig. 2 A) with an overall accuracy of 70% (Fig. 2 B)[10]. The receiver operating characteristic (ROC) curve in figure 2 B lies above the line of unity, signifying the predictive accuracy of the model. The c index (or area under the ROC curve) of 0.70 indicates good degree of discrimination. The model should not, however, be used as a basis for clinical decision making *per se*, but as a tool to complement the decision making process.

Decision curve analysis

A typical prediction model provides the probability of an event, such as the occurrence of DGF, on the basis of a set of risk factors (e.g. CIT and donor age). Prediction models should be evaluated by applying the model to an external validation dataset and comparing the predictions of the model with actual patient outcome. Results are typically

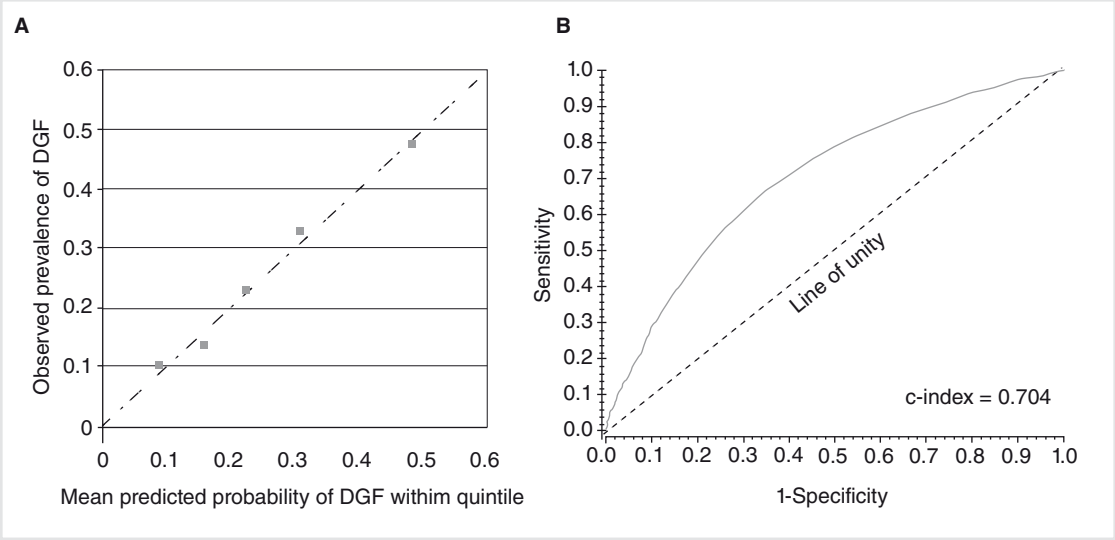

Figure 2. ***A:*** *observed prevalence of delayed graft function (DGF) by mean predictive probability of DGF quintiles. A graph of the observed prevalence of DGF by the mean predicted probability of DGF within DGF risk quintiles. Within each group the mean predicted probability of DGF was calculated (x-axis) and plotted against the observed prevalence of DGF (y-axis) for that group. The plot shows good agreement between the predicted probabilities and the observed prevalence of DGF.* ***B:*** *Receiver operating characteristic curve (ROC) representing the predictive accuracy of the delayed graft function prediction model. The concordance c index (or area under the ROC curve) was 0.704.*

expressed as the area under the ROC (AUC), sensitivity, and specificity. Table 2 provides a brief explanation.

The AUC focuses solely on the predictive accuracy of a model and does not indicate whether the model is worth using at all (e.g. use the DGF model for decision to treat or closer follow-up), or which of selected treatment decisions (e.g. treat all patients or treat none) is preferable. This is because the typical measures of predictive performance do not incorporate information on the consequences of a decision. For example, in a case where the outcome of a false-negative result is much more harmful than a false-positive result, a model with greater specificity but lower sensitivity could have a higher AUC, but would be a poorer choice for clinical use since the decision will have more negative implications

Table 2. Standard measures of model performance: sensitivity and specificity

	Condition (as determined by "gold standard")	
Test/Model Outcome	**Positive**	**Negative**
Positive	True-positive (TP)	False-positive (FP) (Type I error)
Negative	False-negative (FN) (Type II error)	True-negative (TN)
	Sensitivity	Specificity

Sensitivity = TP/(TP + FN). Specificity = TN/(FP + TN). False positive rate = FP / (FP + TN) = 1 – specificity. False negative rate = FN/(TP + FN) = 1 – sensitivity. Power = sensitivity = 1 – false negative rate. Receiver operating characteristic curve (ROC) is a graphical representation of the trade-off between sensitivity and a false-positive rate for different thresholds of probabilities of the event (e.g. probability of delayed graft function in the range 0 to 1). TP: true-positive; FP: false-positive; TN: true-negative; FN: false-negative.

(e.g. suboptimal treatment, complications of unnecessary biopsy, mortality, etc).

Decision analytic methods incorporate consequences and, in theory, can provide information of whether or not a treatment model (or other action) is worth using for treatment (or other action) decisions, or which of several alternative treatment (or action) models should be used[26]. In a typical decision analysis, possible consequences of a clinical decision are identified and the expected outcomes using alternative clinical management strategies are assumed, using estimates of the probability of their occurrence and sequelae of events in a hypothetical cohort of patients. Decision analysis requires explicit valuation of health outcomes, such as the number of complications prevented, life-years saved, or quality-adjusted life-years saved[26]. In a decision analysis of alternative diagnostic or prognostic models, the optimal model is the one that maximizes the outcome of interest[27].

Recent techniques have been proposed to simplify decision-analytic methods by using a risk/benefit ratio to summarize the health outcomes associated with the consequences of testing[27,28]. One technique utilizes the net benefit of a predictive model defined as follows:

$$\text{Net benefit} = \frac{\text{True positive count}}{n} - \frac{\text{False positive count}}{n}\left(\frac{p_t}{1-p_t}\right)$$

Here, the true- and false-positive counts are the number of patients with true- and false-positive results, respectively; n is the total number of patients, and p_t is the clinical decision threshold based on the probability of the event (range: 0 to 1). In the above formula, the proportion of all subjects who are false-positive is subtracted from the proportion of all subjects who are true-positive, weighted by the relative harm of a false-positive and a false-negative result. The relative harm is often defined as the odds of the clinical decision threshold (i.e. $p_t/1- p_t$). A threshold of 10%, for example, means that the false-positive classification is weighted at one ninth of a true-positive classification. The decision to treat or the treatment options may vary for probabilities between 0 and 1, and should be based on clinical judgment.

Using decision curve analysis, the net increase in the proportion of appropriately treated patients over a range of threshold probabilities of DGF (net benefit) is provided in figure 3. Results are based on deceased donor transplant data reported to the US United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) database in 2009. The threshold probabilities represent possible triggers for influencing clinical decision making. Decision curve analysis allows one to vary the threshold probability over an appropriate range. This is important because often either (i) there are insufficient data on which to calculate a rational threshold, or (ii) patients/clinicians may disagree about the appropriate threshold due to different preferences for alternative health states. For example, for a threshold probability of 0.25, the net benefit of the model is 0.066. Using the model is the equivalent of a strategy that identified the equivalent of 6.6 cases of DGF per 100 patients with no unnecessary treatment (i.e. default policy to treat all patients).

The relationship between the hazards of graft failure and the odds of DGF was evaluated using ordinary least squares regression. Based on the results, a mathematical model was derived: HR = OR: 0.387[10], where a two-fold increase in the predicted odds of DGF is associated with a 30% increase in the risk of graft failure, irrespective of whether DGF occurred or not. The formula is used in the following way: if treatment decreases (or increases) the odds of DGF, then we can calculate the anticipated decease (or increase) in the hazards

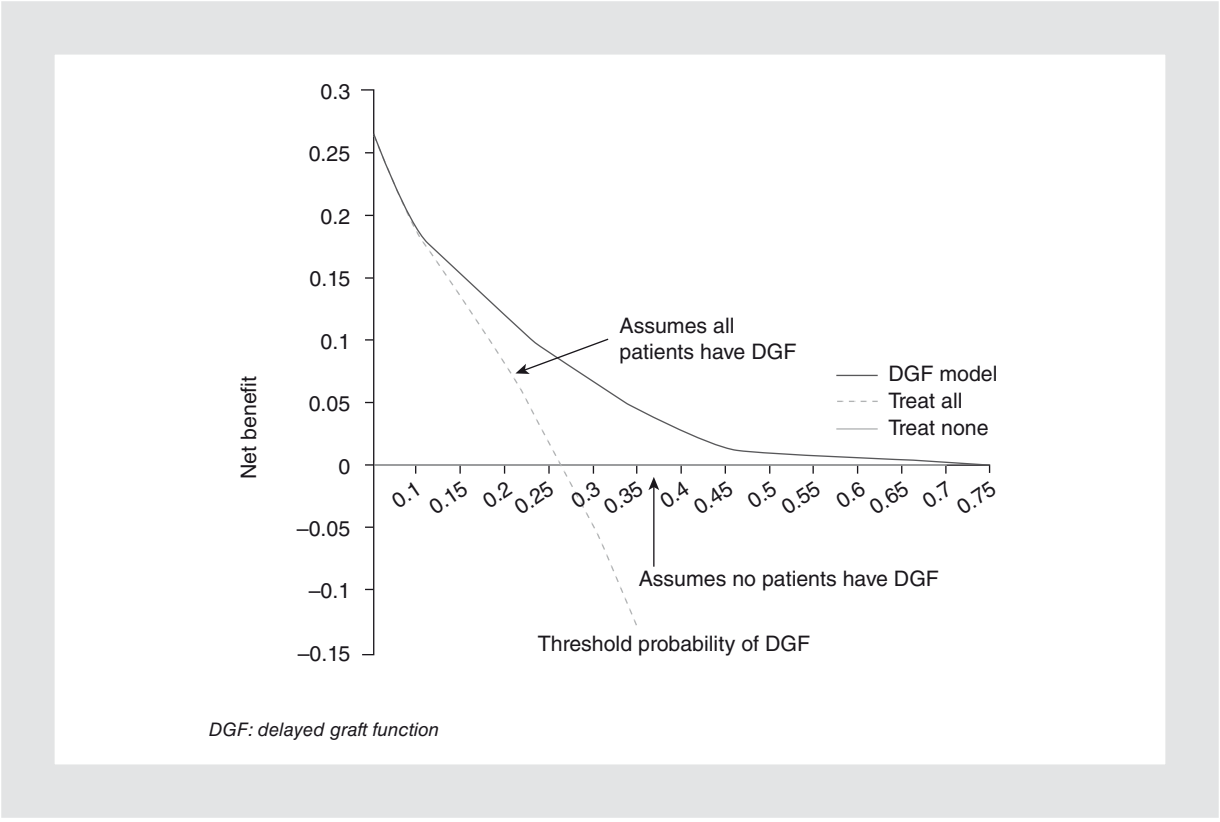

Figure 3. *Decision curve for the predicted probabilities of delayed graft function for deceased donor transplants in 2009. The performance of a prediction model can be summarized as a net benefit of the model over default policies of treat all or treat none. Predicted probabilities of delayed graft function were based on deceased donor data reported UNOS/OPTN in 2009. For a threshold probability of 0.25, net benefit of the model is 0.066. Using the model is the equivalent of a strategy that identified the equivalent of 6.6 cases of DGF per 100 patients with no unnecessary treatment. UNOS/OPTN: United Network for Organ Sharing/Organ Procurement and Transplantation Network.*

rate of graft failure. For example, in a recent study conducted by Moers, et al., machine perfusion was found to decrease the odds of DGF by 28.1% versus static cold storage (OR: 0.719)[11]. This decrease in the odds of DGF with machine perfusion translates into a 12% reduction in the expected hazards of graft failure.

Limitations in prediction

Delayed graft function is typically defined as the need for dialysis within the first seven days post-kidney transplantation. Since the postoperative requirement of dialysis is not standardized and the decision to dialyze is subjective[29], considerable variation in center-specific incidences of DGF exists[30]. As such, it is impossible to uniformly identify diagnoses of true DGF based solely on objective criteria. With this degree of uncertainty, it is unlikely that any statistical model can predict with high degree of accuracy the probability of DGF[29,30].

Machine perfusion use differs by transplant center; therefore, the model did not take this variable into account. Machine perfusion is, however, becoming increasingly common, especially in recipients of expanded criteria donors and donation after cardiac death allografts[10]. In a multicenter clinical trial, Moers, et al. showed that machine perfusion decreased the incidence of DGF by approximately 6% compared to donor organs placed on cold storage (20.8 vs. 26.5%, respectively; OR: 0.57; 95% CI: 0.36-0.88)[11]. When the DGF model

was applied to a cohort of recipients in the UNOS/OPTN database whose donor organs were machine perfused, model-based predictions of DGF tended to overestimate the risk of DGF by approximately 10%[10]. This suggests that in patients whose donor organs were machine perfused, model-based predictions of DGF should be decreased by 10%. In other words, if the predicted probability of DGF for an individual patient is 35% and the recipient's donor organ was machine perfused, then the calibrated probability of DGF for that patient should be 25%. Further research is needed to evaluate the reliability of the calibration factor for DGF risk prediction across a broad spectrum of risk factor categories (e.g. donor age, CIT, etc).

Summary

The updated model provides a useful tool for developing a pretransplant index of the likelihood of DGF in the current era of deceased donor renal transplantation. The model is not perfect. It does not predict with absolute certainty whether a patient will develop DGF – an all-or-none proposition – but only the likelihood of DGF. As a famous statistician once wrote, "All models are wrong, but some are useful". The DGF model could be used as a tool to optimize therapeutic options by identifying kidney transplant recipients who are at increased risk of DGF. In other words, there may be a threshold DGF index above which patients may benefit from different therapeutic strategies. The DGF model could also be used in clinical trials as a means to enrich the study population (inclusion/exclusion criteria), or as a stratification factor where DGF is the primary outcome for drug development (fixed or adaptive allocation). Finally, the DGF index could be used as a surrogate marker of early (and possible late) graft function, although further studies are needed to validate the long-term implications of the DGF risk score.

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